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CHAPTER 17

Respiratory Disease and Pasteurellosis

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In the first edition of *Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery,* pasteurellosis was emphasized as the major cause of respiratory disease in rabbits. That is probably still true in many rabbitries. However, in recent years some *Pasteurella*-free rabbitries have been established. In pet rabbits, pasteurellosis is less common than in past years. *Pasteurella multocida* should always be considered but never assumed to be the only cause of respiratory disease in pet rabbits. Differentiation is crucial.

In the first edition, I summarized the work of Webster and Smith in the 1920s. They established *P. multocida* as the cause of a rabbit respiratory infection ("snuffles") in a large colony of rabbits to be used in research. They also studied epidemiology, virulence of *P. multocida* strains, pathogenesis, and control of the infection. Their conclusions and control methods still guide us. They found that some of the rabbits exposed to the agent (l) resisted infection; (2) spontaneously eliminated infection; (3) became subclinical carriers; (4) developed acute disease (bacteremia or pneumonia); or (5) developed chronic disease. These conclusions also may apply to other bacterial causes of respiratory disease.

Respiratory disease in rabbits is often caused by bacterial agents: *P. multocida, Bordetella bronchiseptica, Staphylococcus* species, *Pseudomonas* species, and other bacteria, or occasionally by viral agents. Noninfectious causes include allergens, nasal or thoracic neoplasia, cardiovascular disease, and exposure to respiratory irritants or trauma. Many more studies involving pasteurellosis have been reported than for any other cause of respiratory disease in rabbits. This chapter presents information about these causes, then discusses the diagnosis and differentiation, treatment, and control of respiratory disease in rabbits.

INFECTIOUS CAUSES

Pasteurellosis

Bacterial and cultural characteristics *P. multocida* is a gram-negative, bipolar, nonmotile asporogenous coccobacillus of the family Pasteurellaceae, which includes *Haemophilus, Actinobacillus,* and *Pasteurella* species (i.e., the HAP group). *P. multocida* grows on blood agar and dextrose starch agar but not on MacConkey's agar. Some strains may require fresh blood for growth on nutrient agar, with cultural characteristics influenced by the type of blood used. Colonies grow larger and produce greenish discoloration on media with horse blood. *P. multocida* produces a distinctive odor, which bacteriologists liken to that of indole. Growth occurs under aerobic conditions or in 5% carbon dioxide. Temperature-sensitive and carbon dioxide–sensitive strains may exist. Most isolates require 24 to 48 hours

of incubation to become apparent on blood agar, especially if mixed with other bacteria. Blood agar with 2 µg/mL of clindamycin can be used to inhibit other bacteria in mixed cultures. Colonies are convex and smooth but vary in coloration from bluish to greenish iridescence when observed in obliquely transmitted light, and they may vary in mucoid appearance. Colonies of the mucoid strains appear to run together, if their numbers permit. Capsular type A strains have large capsules and produce mucoid colonies, whereas colonies of the type D strains may appear iridescent.

P. multocida strains isolated from rabbits usually have the following biochemical characteristics: oxidase+, catalase±, indole±, hydrogen sulfide–, urease–, ornithine decarboxylase+, hexose+, and carbohydrate fermentation+ for most sugars. These characteristics are useful in distinguishing *P. multocida* from other *Pasteurella* species that may be part of the normal flora.[26]

Serotypes Serologic typing is done with the use of indirect hemagglutination, to identify capsular types A, B, D, E, or F, and the gel diffusion precipitin test, which has been used to describe 16 somatic antigen determinants of lipopolysaccharide. The acriflavine flocculation test is specific for capsular type D strains, whereas a staphylococcal hyaluronidase inhibition test specifically inhibits type A strains. With these tests, most isolates from rabbits were shown to be of type A. Serotypes vary by region, but in the United States, A:12 and A:3 are the most prevalent types.[22]

Okerman and co-workers[24] substantiated the conclusion of Webster and Smith that some strains of *P. multocida* are more pathogenic than others. Capsular type D isolates from rabbits with bacteremia are significantly more pathogenic for mice than are type A isolates from rabbits with rhinitis only. Somatic type 3 isolates are more pathogenic than type 12 isolates.[22]

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) provides enhancement of differentiation among *P. multocida* isolates from rabbits.[11] Single-primer polymerase chain reaction (PCR) fingerprinting is efficient and reproducible for discriminating *P. multocida* isolates.[10]

Virulence factors Virulence factors of *P. multocida* include adhesions, phagocyte resistance, endotoxin (lipopolysaccharide), exotoxin, and iron regulation. Pili or other adhesion proteins on the outer membrane of some strains of *P. multocida* enhance colonization. Type A strains are more adhesive to respiratory mucosa than are type D strains. Invasion and multiplication of the organism occur because the capsule, largely consisting of hyaluronic acid, which also is present in host tissues, inhibits phagocytosis and complement-activated bactericidal activity of serum (opsonization). Some type D strains, although ingested by phagocytes, resist bactericidal activity. Leukotoxic enzymes also are produced. Growth of some strains of *P. multocida* is regulated by the availability of iron, and most strains produce iron-binding outer membrane proteins, which enhance their survival in iron-poor cavities of the hosts.

Serotype D:1 strain (noncapsulated, fimbriae+, hemagglutination [HA]+, dermonecrotic toxin [now termed *P. multocida* toxin, or PMT]+) was highly adherent to tracheal mucosa, lung, and aorta explants when compared with serotype A:3 (capsulated, fimbriae+, HA–, and PMT–), although A:3 adhered after prolonged incubation. Adhesion to endothelial receptors may explain association of some strains with pneumonia and septicemia.[2]

Endotoxin enhances resistance to bactericidal activity of serum and stimulates the release of inflammatory mediators, such as interleukin-1. In cases of bacteremia, free endotoxin in plasma causes fever and depression and may induce shock. A toxin with characteristics of an exotoxin is produced by some strains of *P. multocida*. PMT of some type D strains enhances attachment and colonization of mucosa. This protein toxin, which is similar to that causing atrophic rhinitis in pigs, also is associated with nasal turbinate atrophy in rabbits. Toxin has been demonstrated for type D[26] and for type A isolates,[15] but it is not clear whether it is the same toxin. Purified PMT induces pneumonia, pleuritis, lymphoid atrophy, and possibly osteoclastic bone resorption in rabbits.[6]

Antibiotic sensitivities Antibiotic sensitivities for 42 isolates of *P. multocida* from rabbits are as follows: 100% were sensitive to chloramphenicol, erythromycin, novobiocin, oxytetracycline, penicillin G, nitrofurazone, and nitrofurantoin; most were resistant to sulfonamides and streptomycin; and all were resistant to lincomycin and clindamycin. In my laboratory, four strains of *P. multocida* from rabbits were resistant to erythromycin and had moderate or intermediate sensitivity to penicillin G but otherwise were sensitive to 16 antibiotics, including several fluoroquinolones and cephalosporins. In my practice, most isolates of *P. multocida* tested on Mueller-Hinton agar with 5% sheep blood have been sensitive to amikacin, chloramphenicol, ciprofloxacin, doxycycline, enrofloxacin, gentamicin, penicillin G, tetracycline, and trimethoprim-sulfa.

Transmission and pathogenesis Transmission of *P. multocida* is by aerosol from acutely affected rabbits, by direct contact, or by fomites.[22] Venereal transmission also occurs with genital infections, and kits may be infected at birth if the doe has genital infection. However, kits usually remain uninfected for several weeks, and the prevalence of infection increases with age and exposure.

P. multocida gains entry to the host primarily through the nares or wounds. If the host does not resist infection, the bacteria colonize the nares and may cause production of nasal exudate. The incubation period is difficult to define because many rabbits are subclinical carriers of infection; however, in experimental studies, rhinitis occurred 1 to 2 weeks after intranasal inoculation of *P. multocida*. Once established in the nasal passages, infection spreads to contiguous tissues (paranasal sinuses, nasolacrimal duct and conjunctiva, eustachian tube and middle ears, trachea, bronchi, and lungs). Hematogenous spread also accounts for infection that reaches the middle ears, lungs, and internal organs.

Most of the Pasteurellaceae are commensal organisms on mucous membranes but exhibit pathogenicity under conditions of immunodeficiency and stress in the host. Nutritional, environmental, managerial, or social changes may predispose to disease, as may concomitant infection and physical or chemical injury to the mucosa. Exposure of mucous membranes to ammonia or dilute acetic acid increases the susceptibility of rabbits to *P. multocida* infection, and stress or hydrocortisone treatment increases pathogenicity. With disseminated pasteurellosis, fever enhances the neutrophil response and increases survival.

The protective role of the humoral immune response to *P. multocida* is unclear. Immunization partially protects against severe disease but does not prevent infection.[22] Antibodies to antigens of *P. multocida* or to cross-reacting antigens of other bacteria may enhance opsonization and phagocytosis. Common

epitopes do occur between *P. multocida* and other gram-negative bacteria, notably *Pasteurella, Yersinia,* and *Moraxella* species.

Antibodies to gram-negative core antigens occur in rabbits and increase with age, indicating possible cross-reactive epitopes between *P. multocida* and Enterobacteriaceae and possible protection against pasteurellosis.[28] An *Escherichia coli* J5 bacterin induced antibodies and reduced bacteremia in rabbits challenged with *P. multocida*, but was not protective against colonization.[27] *P. multocida* serotype A:3 was shown to attach to and invade epithelial cells, causing deciliation of ciliated cells and hyperplasia of goblet cells of nasal mucosa; thickening of alveolar septa; swelling of capillary lining cells; and infiltration of inflammatory cells in the lungs.[2,3] Thrombocytosis is a consistent secondary response to *P. multocida* infection; however, it does not appear to be predictive of disease outcome.[29]

Serum with immunoglobulin G (IgG) to *P. multocida* is not bactericidal in vitro or in vivo.[22] Rabbits with chronic and severe infections usually have high IgG titers to *P. multocida*. Also, the secretory immune response (IgA) does not protect against nasal infection,[12] although it may play a role in limiting spread. The protective role of cell-mediated immunity in *P. multocida* infection has not been well studied, but depressed T-lymphocyte function results in severe disease in infected rabbits.

Vaccine strategies No vaccine is currently available for the prevention of pasteurellosis in rabbits. The following vaccine preparations have been evaluated and have *not* prevented nasal infection on challenge: bacteria killed with heat or formalin; potassium thiocyanate extracts; and live but avirulent strains, such as a streptomycin-dependent strain.[22] Characterization of the protein patterns and immunogenic epitopes of *P. multocida* by electrophoresis and immunoblotting indicates that several proteins are consistently recognized by the immune systems of infected rabbits.[13,39] Several antigens associated with virulence have been identified, offering promise for their use in subunit vaccines. Specific antiserum to an outer membrane 87-kDa antigen protected mice against lethal challenge.[30] Cloning and sequencing of subunit proteins associated with virulence (fimbriae, capsule, transferrin binding, hemolysis) may lead to potential vaccine candidates.[1] Immunization with inactivated, purified PMT stimulated a protective response to PMT challenge that was enhanced by coadministration of cholera toxin (CT), a potent adjuvant for the mucosal immune system.[19] When CT was administered with potassium thiocyanate extract (PTE) of *P. multocida*, protective immunity to pasteurellosis was enhanced in rabbits.[32] Intranasal immunization with both inactivated purified PMT and PTE induced a protective response against homologous *P. multocida* challenge.[31] Use of oral or intranasal delivery of microencapsulated antigens (PTE) also enhanced protection, as evidenced by production of anti-PTE IgA and IgG as well as decreasing severity of infection after challenge. Coadministration of CT did not improve protection when used with the microencapsulated PTE.[33]

Clinical and pathologic manifestations The clinical presentation of pasteurellosis in rabbits includes upper respiratory tract disease (rhinitis, sinusitis, conjunctivitis, lacrimal duct infection), otitis, pleuropneumonia, bacteremia, and abscesses of the subcutaneous tissues or internal organs, bones, joints, and genitalia.

Upper respiratory tract disease Upper respiratory tract disease (snuffles) in rabbits is often caused by *P. multocida;* however, predisposing factors influence pathogenicity. Rhinitis and sinusitis are the most common forms of pasteurellosis. A serous nasal discharge precedes the typical white or yellowish mucopurulent discharge associated with *P. multocida*. Exudate adheres to the fur around the nares (Fig. 17-1), and, because rabbits groom the face with their forepaws, to the medial aspects of the forepaws, where it mats and becomes yellowish-gray on drying. Affected rabbits often make audible sonorous noises and have bouts of sneezing, with exudate forcibly expelled from the nares. Conjunctivitis is sometimes a manifestation of upper respiratory tract disease. Infection of the nasal lacrimal duct may extend to the conjunctiva. Exudate occluding the duct causes excessive tearing and scalding of the face, alopecia, and pyoderma.

Auscultation of the trachea and nares reveals rales and rattles caused by exudate in the upper respiratory tract. The origin of these respiratory sounds must be determined so that rales from the lungs are not misinterpreted. Signs of rhinitis may subside or even disappear, with affected rabbits harboring infection in the paranasal sinuses or middle ears. Recovery from acute disease and elimination of infection may occur, but spontaneous recovery from chronic infection is unlikely.

Acute infection of the nares is accompanied by edema and hyperemia of the mucosa. Chronic infection may be accompanied by mucosal erosion and atrophy of the turbinates.

Otitis Extension of the infection from the nares to the middle ears probably occurs through the eustachian tubes. Most rabbits with otitis media also have rhinitis, but some clear the infection from the nares while the middle ears remain infected.[12] Otitis media may be asymptomatic, or, if infection spreads to the inner ear, torticollis, nystagmus, and ataxia can occur. Infection extends to the external ear if the tympanic membrane ruptures. What appears to be accumulation of wax deep in the ear canal may be dried exudate, which, if removed, reveals the typical white, purulent exudate underneath. Exudate may be physically expressed by gentle pressure at the base of the ear, and its origin can be determined by otoscopic examination. Consider otitis media in a rabbit that scratches excessively at the base of the ear but has no external parasites or when an abscess is detected at the base of the ear. A dorsoventral radiograph of the skull aids in diagnosis of otitis media; increased soft tissue opacity caused by the exudate can be visualized within the bulla, and the bone

Figure 17-1 Severe rhinitis and nasal exudate in a rabbit infected with *Pasteurella multocida*. Note the exudate around the nares.

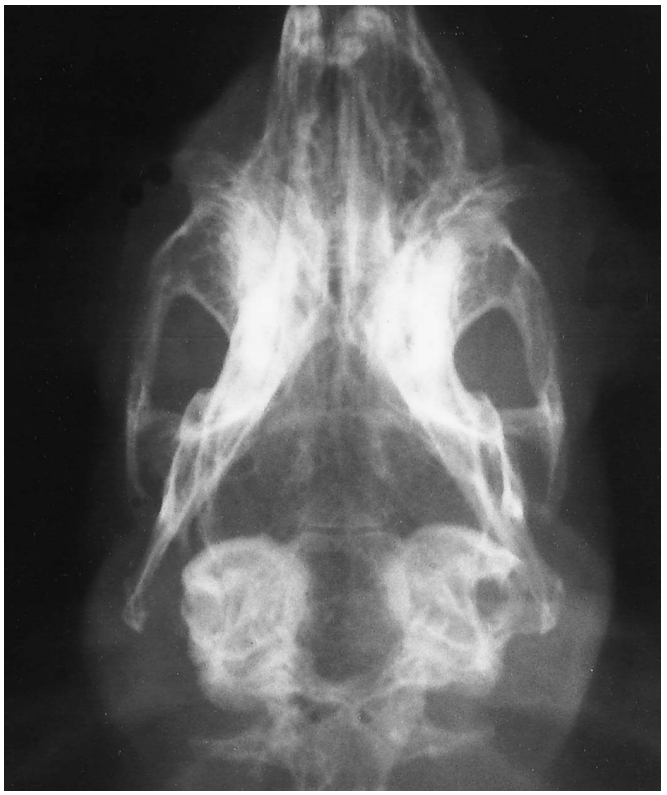


Figure 17-2 Dorsoventral radiograph of the skull of a Holland lop rabbit with exudate in the ear canals. Increased density and thickening of the tympanic bullae indicates bilateral otitis media.

shows thickening (Fig. 17-2). The tympanic bullae are normally thin-walled and hollow.

Bacteremia The more pathogenic strains of *P. multocida* are likely to spread hematogenously, causing acute generalized disease, fever, and sudden death. Pathologic examination may reveal congestion, petechiation, and microscopic abscesses throughout the viscera. Pleuropneumonia is another sequela of hematogenous spread.

Pneumonia, pleuritis, pericarditis Chronic infection within the thoracic cavity may go undetected until long after the acute phase of infection (Fig. 17-3), and it is likely to take the form of pleuropneumonia or pericarditis, with abscesses developing in or around the lungs or heart (Fig. 17-4). Anorexia, weight loss, depression, and rapid fatigue are nonspecific signs, but in rabbits they should arouse suspicion of lower respiratory tract disease. Dyspnea occurs on exertion. Auscultation may reveal areas in the thorax in which lung sounds are absent because of consolidation or abscess. Pulmonary rales must be differentiated from those referred from the upper respiratory tract. Radiographs help to determine the extent of involvement. Rabbits often appear relatively normal, even with minimally functioning lungs.

Pathologically, pasteurellosis in the thorax is characterized by the presence of fibrinopurulent exudate in the airways and on serosal surfaces. Neutrophils (also called heterophils) are the principal inflammatory cells, but macrophages and erythrocytes may be present. Lymphocytic peribronchial and perivascular cuffing also occur.

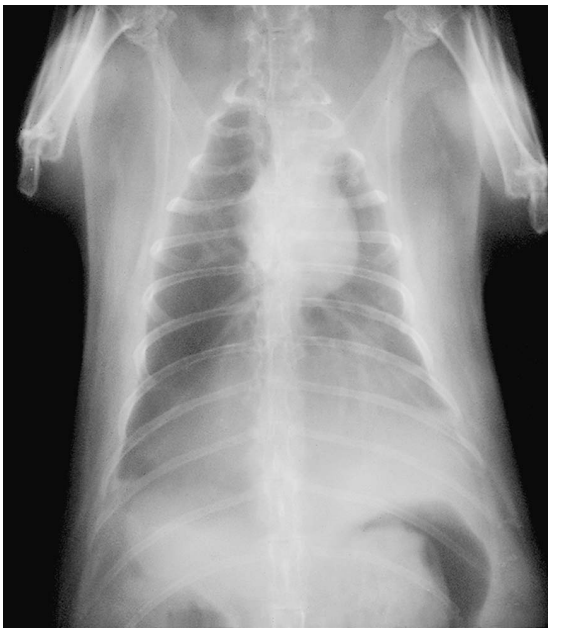


Figure 17-3 Dorsoventral radiograph of the thorax of a rabbit with pulmonary rales resulting from a chronic bronchopneumonia. Note increased peribronchial density.

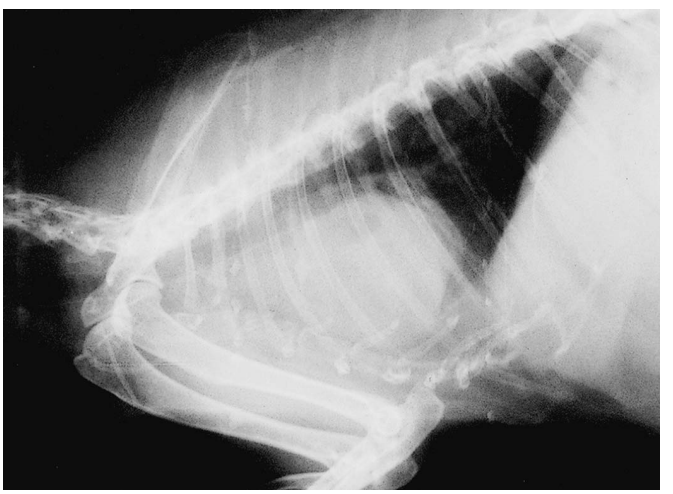


Figure 17-4 Lateral radiograph of the thorax of a rabbit with respiratory distress and bradycardia caused by pericarditis and abscess anterior to the heart. Note dorsal tracheal deviation. *Pasteurella multocida* was isolated from the abscess.

Abscesses and genital infections Abscesses in subcutaneous tissues, retrobulbar tissues, or the internal organs of rabbits frequently are caused by *P. multocida*. These abscesses are well encapsulated, contain thick white exudate that does not drain, and enlarge slowly. Mandibular abscesses and infections of the hock joints are common. Genital tract infections occur in both males and females; pyometra is common. Occasionally wound infections caused by *P. multocida* result in cellulitis rather than an abscess. Cellulitis is more difficult to treat than an abscess, and antibiotic sensitivity testing becomes even more important.

Abscesses in rabbits tend to appear similar regardless of cause, and not all are caused by *P. multocida*. For example, I have cultured the following organisms in pure culture from abscesses that appeared as described: *Pseudomonas aeruginosa* and *Peptococcus* species from mandibular abscesses, *Staphylococcus aureus* from a pericardial abscess, and *Enterococcus* species from a joint abscess. It is important to document the bacterial pathogen and antibiotic sensitivity and not to assume that the cause is *P. multocida*.

Bordetella bronchiseptica

B. bronchiseptica is a common inhabitant of the respiratory tract of rabbits. The prevalence of infection increases with age, and both nares and bronchi become colonized. There is an inverse relationship between *B. bronchiseptica* and *P. multocida* in rabbitries: weanlings have higher rates of infection with *B. bronchiseptica*, whereas *P. multocida* usually predominates in adults.[12] Experimentally, intranasal inoculation of *B. bronchiseptica* caused serous nasal discharge, bronchopneumonia, and pleuritis in suckling or weanling rabbits.[17] Sinusitis and bronchopneumonia due to *B. bronchiseptica* resulted when local host defense was reduced.[4]

B. bronchiseptica is pathogenic in guinea pigs, dogs, cats, and pigs. It adheres to ciliated mucosa, resists respiratory clearance, induces ciliostasis, and reduces macrophage adherence and phagocytosis.[38] Cytotoxic *B. bronchiseptica* enhances colonization by toxigenic *P. multocida*.[16] Therefore *B. bronchiseptica* is suspected as a copathogen or predisposing factor in *P. multocida* infections. More pathogenic strains of *B. bronchiseptica* may exist. For example, an investigation of upper respiratory tract infections in rabbits from a colony of inbred rabbits showed them free of *P. multocida;* however, the nares were colonized by *B. bronchiseptica*, which was resistant to several commonly used antibiotics (B. J. Deeb and R. DiGiacomo, unpublished data). Clinically, I have seen numerous cases of rhinitis associated with pure cultures of *B. bronchiseptica*. In such cases, selective antibiotic therapy for *B. bronchiseptica* is indicated.

Staphylococcus aureus

S. aureus is often isolated from the nares of both healthy and diseased rabbits. It is probably a secondary agent that increases suppurative inflammation of compromised mucosa. As with *P. multocida* infection, pathogenicity depends on host susceptibility and bacterial virulence. *S. aureus* produces toxins that are lethal for rabbit neutrophils as well as protein A, which binds the crystallizable fragment (Fc) of IgG. By these means, bactericidal mechanisms of the host are blocked.[8]

Disseminated staphylococcosis results in fibrinous pneumonia or abscesses in the lungs or heart. Abscesses caused by *S. aureus* appear similar to those caused by *P. multocida*, but *S. aureus* more often shows in vitro resistance to a variety of antibiotics than does *P. multocida*. Therefore a culture and sensitivity test is advisable if the abscess is in an accessible area. Chloramphenicol, enrofloxacin, and trimethoprim-sulfa combinations are antibiotics of choice for rabbits when a culture specimen cannot be obtained.

Pasteurella Species

Pasteurella species other than *P. multocida* are often cultured from nasal swab samples of rabbits. Unless the organism is present in pure culture and is associated with clinical disease, it is probably a commensal organism rather than a pathogen.

Moraxella catarrhalis

Moraxella catarrhalis, previously known as *Micrococcus, Neisseria*, or *Branhamella catarrhalis*, is a well-represented member of the nasal flora of rabbits. Like *B. bronchiseptica,* it is sometimes isolated from rabbits with rhinitis or conjunctivitis. If isolated in pure culture, the organism may have a role in the disease, probably as an opportunist on unhealthy mucosa. However, unless clinical disease is present, antibiotic therapy is not justified to eliminate *M. catarrhalis* from the nares.

Other Bacteria

Other bacterial agents that have caused pneumonia in rabbits are *Mycobacterium bovis, Mycobacterium tuberculosis, Francisella tularensis, Yersinia pestis, Moraxella bovis, E. coli,* and *P. aeruginosa*. Tularemia is rare in domestic rabbits. *P. aeruginosa* can cause abscesses similar to those of *P. multocida,* as well as septicemia and pneumonia.

Cilia-associated respiratory (CAR) bacillus colonizes ciliated epithelial cells of the respiratory tract and causes chronic respiratory disease in rodents. Although it occurs in rabbits, CAR bacillus induces only mild hyperplasia of ciliated epithelium and inflammatory infiltration.[9,20]

Mycoplasma/Chlamydia

In 1967, I isolated *Mycoplasma pulmonis* from the nasopharynx of rabbits with signs of upper respiratory tract disease. Specimens from the rabbits were not cultured for *P. multocida*. The rabbits were housed in close proximity to rats, which may have been the source of the infection. *M. pulmonis* causes chronic respiratory disease in rats, but the pathogenicity of *M. pulmonis* in rabbits has not been investigated. Isolation of *Mycoplasma* species requires special media and methods and precludes routine examination for these organisms. In 1986, I attempted to isolate *Mycoplasma* species from the nasopharynx and lungs of 52 rabbits from four commercial rabbitries where respiratory disease was endemic. *Mycoplasma* species were not recovered (unpublished data).

Chlamydia species have been isolated from the lungs of domestic rabbits with pneumonia. A mild interstitial pneumonia occurred when the agent was inoculated into the trachea of laboratory rabbits.

Viruses

Viral agents of respiratory disease in rabbits are not well studied; they may be insignificant as pathogens in the respiratory tract, or they may be underreported.[14]

Myxoma virus causes nasal and ocular discharge and dyspnea in protracted cases. However, respiratory disease is not a hallmark of myxomatosis and is not likely to occur in the absence of generalized disease, edema, and tumors. Myxoma virus causes acute hemorrhagic pneumonia.[23]

A herpesvirus has been recovered from the nares of European rabbits with respiratory disease.[14] Rabbits have also developed

antibodies to Sendai virus, a paramyxovirus that causes respiratory disease in rodents. However, experimental inoculation did not induce disease in rabbits.

A coronavirus has been implicated in association with pleural effusion and infectious cardiomyopathy.[14] The disease occurred in the 1960s in Scandinavia in rabbits used to propagate *Treponema pallidum*. Because no cases of the disease outside the laboratory environment have been reported, the agent may have been a contaminant of suspensions of testicular cells infected with *T. pallidum*. The target organ of the viral agent was the heart. Clinical signs were those typical of acute viremia and, in survivors, of myocarditis and congestive heart failure.

NONINFECTIOUS CAUSES

Immunologic Causes

Rhinitis, conjunctivitis, and chronic bronchitis resulting from exposure to allergens occur in rabbits. If the allergen cannot be identified and eliminated from the rabbit's environment, corticosteroids or antihistamines are used to reduce and control inflammation. Pasteurellosis or infections with other pathogenic agents must be ruled out. Prolonged use of corticosteroids in rabbits with chronic *P. multocida* infection is contraindicated.

Neoplastic Disease

Carcinoma of the nasal turbinates causes disruption of the normal architecture of the upper air passageways. Sneezing and nasal discharge accompany the disease, which is usually unresponsive to antibiotics.

Thymomas are often seen in both young and adult rabbits (see Chapter 21). These tumors can be of either lymphoid or epithelial origin. Clinical signs include tachypnea and moderate to severe dyspnea. Bilateral exophthalmos is occasionally observed[36] and may be related to interference of vascular return to the heart caused by the mass. Radiographs reveal a rounded, soft tissue opacity cranial to the heart, dorsal tracheal deviation, and caudal displacement of lungs (Fig. 17-5). Removal of a thymoma via median sternotomy has been accomplished.[7]

Metastases may reach the lungs from tumors in other sites in the body (Fig. 17-6). The rabbit becomes increasingly dyspneic with time. Antibiotics and bronchodilators may help relieve respiratory distress caused by neoplasia, but only temporarily.

Cardiovascular Disease

Pulmonary edema, the accumulation of fluid in the interstitial tissue, alveoli, and bronchi, occurs in conjunction with circulatory disorders. Pulmonary edema in rabbits may be fairly common. Cardiomyopathy and arteriosclerosis are often diagnosed in pet rabbits because their life span is extended (more than 10 years is common). Differentiation from infectious processes involves auscultation of the lungs for typical wheezing sounds, radiographic evaluation, ultrasonography, and hematologic testing. If heart murmurs or arrhythmias are detected, an electrocardiogram or echocardiogram is indicated (see Chapter 21). Treat cardiovascular disease with diuretics, bronchodilators, enalapril, and/or digoxin as indicated.

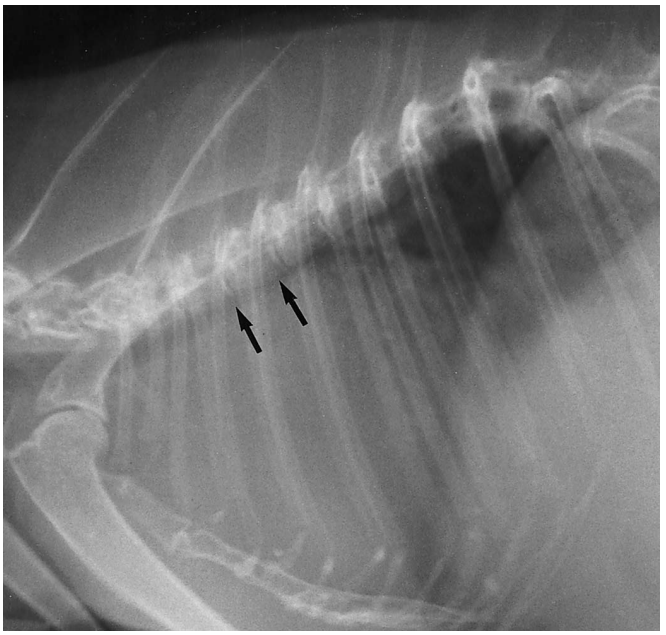


Figure 17-5 Thoracic radiograph from a rabbit with respiratory distress and bilateral exophthalmos, which became pronounced when the rabbit was stressed. A cranial mediastinal mass has caused dorsal tracheal deviation *(arrows)* and border effacement of the cardiac silhouette. The histopathologic diagnosis was thymoma.

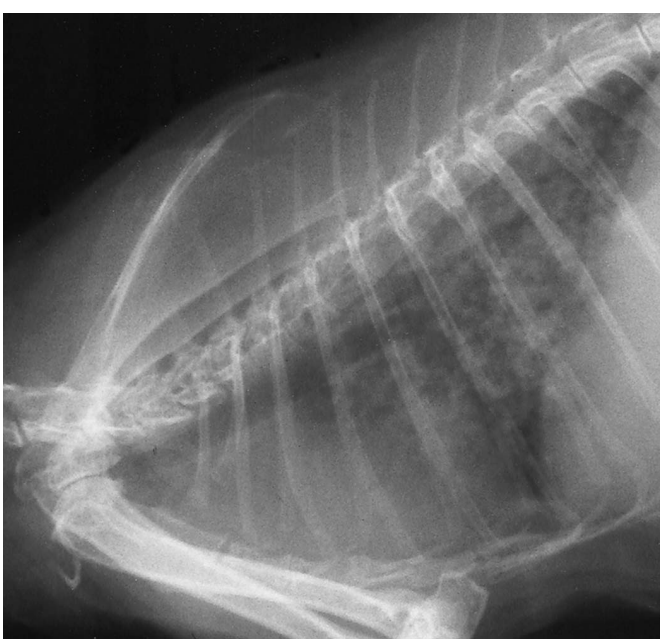


Figure 17-6 Lateral radiograph of the thorax of a rabbit with respiratory distress. Diffuse pulmonary densities resulted from carcinoma metastases.

Traumatic Causes

Traumatic tracheitis may result from endotracheal intubation for inhalant anesthesia. Rabbits maintained for 3 to 4 hours on halothane developed severe necrotizing tracheitis, submucosal edema, and mucosal erosion where the tip of a Sheridan cuffed

endotracheal tube touched the trachea. Use a soft, pliable silicone endotracheal tube or face mask when administering gas anesthesia to rabbits.

Irritation to the respiratory tract occurs with aerogenous exposure to chemicals, such as excessive ammonia from urine buildup, cigarette smoke, and possibly vapors from wood shavings used for litter. Such exposure may predispose the mucosa to infection.

Foreign materials can accidentally gain entry to the nares, pharynx, or trachea (Fig. 17-7). Severe upper respiratory tract rales and respiratory distress result. Open-mouth breathing in a rabbit indicates an emergency, sometimes necessitating oxygen therapy and an immediate attempt to find and remove the airway obstruction. Although rabbits do not normally vomit, postmortem examination in my laboratory has confirmed several cases of food aspiration, probably caused by regurgitation.

DIAGNOSIS AND DIFFERENTIATION

Physical Examination

Examine the rabbit's general appearance; look for evidence of nasal discharge, matted forepaws, and dyspnea; note the color of the mucous membranes. Auscultate the heart and lungs, and listen for nasal and pharyngeal sounds. Determine the origin of respiratory rales and whether they are heard primarily on inspiration or expiration. Absence of lung sounds or very loud heart sounds, or both, may indicate replacement of normal lung tissue with abscesses or neoplasia. Heart murmurs or arrhythmias may be detected on auscultation. Bradycardia may be more indicative of cardiomyopathy than tachycardia in a frightened rabbit (normal heart rate is 180 to 220 beats/min).

Although rhinitis, conjunctivitis, or respiratory distress in rabbits is suggestive of pasteurellosis, a causative diagnosis cannot be made on the basis of clinical signs alone.

Hematologic evaluation is recommended, but hematologic values are not always indicative of infection. Neutrophilia or a shift in the normal neutrophil : lymphocyte ratio (about 2 : 3) is suggestive of bacterial infection. Abnormal biochemical values help detect organ failure.

Table 17-1 outlines the differentiation of respiratory disease in rabbits.

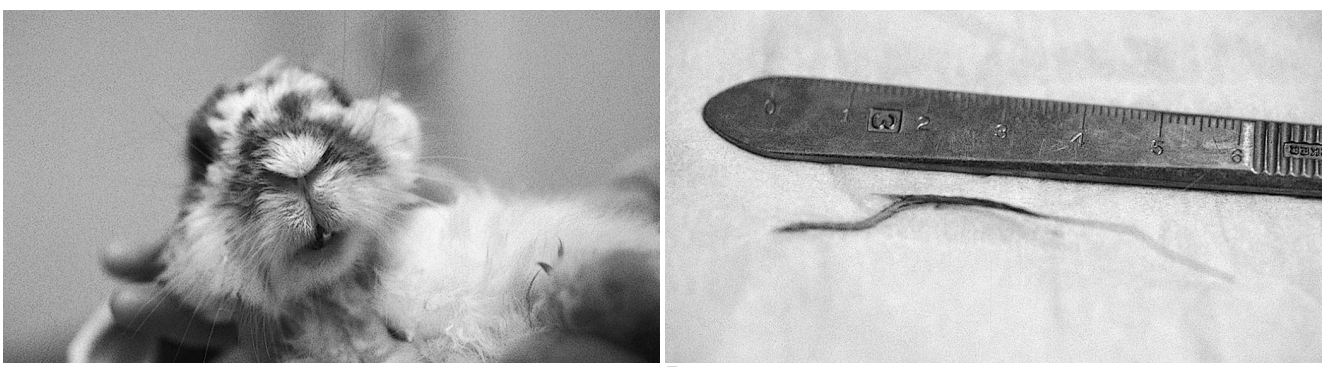
Isolation of Bacteria

Isolation of the causative agent from affected tissues requires culture before the use of antibiotics. Once antimicrobial therapy has been initiated, bacteria may be attenuated, if not eliminated, and difficult to grow in vitro. To determine whether a bacterial pathogen is present in the nares, in the case of rhinitis or in screening for *P. multocida,* insert a No. 4 calcium alginate swab 1 to 4 cm into the nares along the nasal septum on both sides (nasal infection may be unilateral). The nasopharynx may be a better site to recover a pathogen, but it is less accessible. A bacterial agent causing rhinitis is likely to be present in almost pure culture from the nares. There is no need to do multiple sensitivity tests on normal nasal flora in a mixed culture.

For various reasons, *P. multocida* is sometimes difficult to recover, and more than one attempt should be made before ruling it out. To maximize success, the swab of the affected tissue should be inoculated directly or within a short period onto a blood agar plate. If the specimen must be transported to a laboratory, Cary-Blair transport medium is recommended. Incubate the culture for at least 48 hours for the best visualization of the slowly growing *P. multocida* colonies. Some strains grow better in 5% carbon dioxide, and some grow better at 93.2°-95.0°F (34° to 35°C), a temperature range that approximates that in rabbit nares. When collecting a swab sample from an abscess for culture, insert the swab against the inner wall of the capsule, because the centers of abscesses are often sterile. Abscesses in rabbits, especially those associated with infected tooth roots, are sometimes caused by anaerobic bacteria, which will not grow on blood agar plates incubated with oxygen.

Serodiagnosis of *Pasteurella multocida*

Because rabbits infected with *P. multocida* develop antibodies but usually remain infected, serologic testing is helpful in detecting internal infections or subclinical carriers. Enzyme-linked immunosorbent assays (ELISAs) have been developed to detect immunoglobulins against *P. multocida*.[26] ELISAs are reliable in



A **B**

Figure 17-7 **A,** Upper respiratory tract disease and mouth-breathing in a 6-year-old Holland lop. **B,** A piece of hay was recovered from the nares 3 weeks after signs appeared.

TABLE 17-1
Differentiation of Respiratory Disease in Rabbits

Procedure/Findings	Diagnosis
Physical examination	
Sneezing, snoring	URT involvement
Nasal discharge	URT involvement
Matted fur on face and forepaws	URT involvement
Fever or normal temperature	URT involvement
Anorexia, weight loss	LRT involvement
Depression, fatigue	LRT involvement
Dyspnea	LRT involvement
Mucous membranes pale or cyanotic	LRT involvement
Fever or hypothermia	LRT involvement
Auscultation	
Nasopharyngeal rales, pulmonary sounds normal	Rhinitis/sinusitis
Pulmonary rales	Bronchopneumonia
Friction sounds	Pleuritis
Absence of sounds	Thoracic mass or masses
Fluid sounds	Pulmonary edema
Loud heart sounds	Thoracic mass/ cardiomegaly
Radiography	
Increased opacity in nasal turbinates/sinuses	Infection
Bronchial pattern	Bronchitis
Effusion line	Pleuritis, neoplasia
Masses (mediastinal or pulmonary), tracheal elevation	Abscess/neoplasia
Generalized increase in pulmonary opacity	Edema
Cardiomegaly	Cardiomyopathy
Lysis of turbinates/bone	Neoplasia/infection
Interstitial pattern	Pneumonia
Other tests	
Culture from nares	—
CBC, serologic testing for *Pasteurella multocida*	—
Guided needle aspiration/cytology	—
Electrocardiogram	—

CBC, Complete blood count; *LRT,* lower respiratory tract; *URT,* upper respiratory tract.

screening for *P. multocida* infection in rabbits[37] (Table 17-2), but the practitioner must understand the limitations of these tests and not misinterpret results. High levels of antibody to *P. multocida* correlate well with chronic infection. The test does not detect antibody very early in infection, because it takes 2 to 3 weeks for the titer to rise substantially. Antibody in a rabbit younger than 8 weeks of age is probably maternally acquired. Sera with antibodies to related bacteria, possibly normal flora, react at low levels in the test, giving false-positive results. Immunosuppression results in decreased antibody and possibly false-negative results. If a serum sample is reactive at a low level, testing of a second sample about 3 weeks later helps in determining whether the antibody level is increasing (early infection), decreasing (maternal antibody or infection eliminated), or remaining about the same (probably because of infection with related bacteria that are not necessarily pathogenic). The ideal test would be one that detects antibody to an antigenic epitope that is unique to *P. multicoda*,[39] present in all strains, and associated with protective antibodies.[21] A 37-kDa antigen was shown to be a major immunogen during *P. multocida* infection in rabbits. Monoclonal antibody against this antigen, used in a capture enzyme immunoassay, was shown to be sensitive and specific in identifying rabbits infected with *P. multocida*.[25]

Imaging

Radiographs of the head are useful in providing information about the nares, sinuses, and middle ears. Careful dorsoventral positioning is necessary for accurate interpretation of radiographs. Comparison with radiographs of the normal respiratory tract is helpful (Fig. 17-8). Increased density in tympanic bullae, nares, or sinuses indicates infection (see Fig. 17-2). Decreased density occurs in advanced infection if atrophic rhinitis and sinusitis exists or if bone lysis has occurred because of nasal carcinoma.

Thoracic radiography helps differentiate pneumonia, cardiovascular disease, and neoplasia. In bronchitis, thickened bronchial walls appear as "doughnuts" when viewed on end. An interstitial or alveolar pattern of increased density occurs with pneumonia (see Fig. 17-3). Cardiomegaly and a generalized increase in pulmonary opacity can be observed in cardiac disease. A mediastinal mass or multiple pulmonary nodules are indicative of neoplasia but could be confused with abscesses (see Figs. 17-4 and 17-6). Ultrasonography offers the advantage of guided needle biopsy of lesions. Thoracocentesis and cytology are indicated if pleural fluids are apparent.

TREATMENT

Identification of the bacterial agent associated with respiratory disease is important but not always possible. Do not assume *P. multocida* is the cause. Other bacterial agents are more likely to have antibiotic resistances.

Studies for determining the effectiveness of various antibiotics in treating *P. multocida* infection usually have involved rabbits with chronic disease. Results of these studies have shown diminution or cessation of clinical signs during treatment for 7 to 14 days but recurrence after treatment was discontinued, as well as a failure to eliminate infection. Infection was eliminated in seven of eight rabbits treated with enrofloxacin (5 mg/kg SC q12h) for 14 days.[5] Enrofloxacin given in the drinking water (50-100 mg/L) before and continuing for 48 hours after inoculation with a virulent strain of *P. multocida* protected rabbits against bacteremia, provided that daily intake of the drug was greater than 5 mg/kg. Kits from enrofloxacin-treated does were free from *P. multocida* infection, although the infection was not eliminated in the does.[34] Ciprofloxacin (20 mg/kg PO q24h) for 5 days

Table 17-2
Antibodies Against *Pasteurella multocida* in Pet Rabbits*

	Interpretation of Optical Density Readings							
	Negative		Suspicious/Equivocal		Positive		Total	
Age (yr)	*n*	URD	*n*	URD	*n*	URD	*n*	URD
<1	44	19	64	16	251	51	359	86
≥1	408	77	309	51	625	98	1342	176
Total (% with URD)	452	96 (21)	373	67 (18)	876	99 (11)	1701	262 (15)

n, Number tested; *URD*, number with nasal and/or ocular discharge (upper respiratory tract disease).
*As determined by an enzyme-linked immunosorbent assay. Data were collected over a 5-year period on sera submitted by veterinarians in the United States; includes only samples for which clinical signs were listed. Tests were performed by Sound Diagnostics, Inc., 1222 NE 145th, Shoreline, WA 98155.

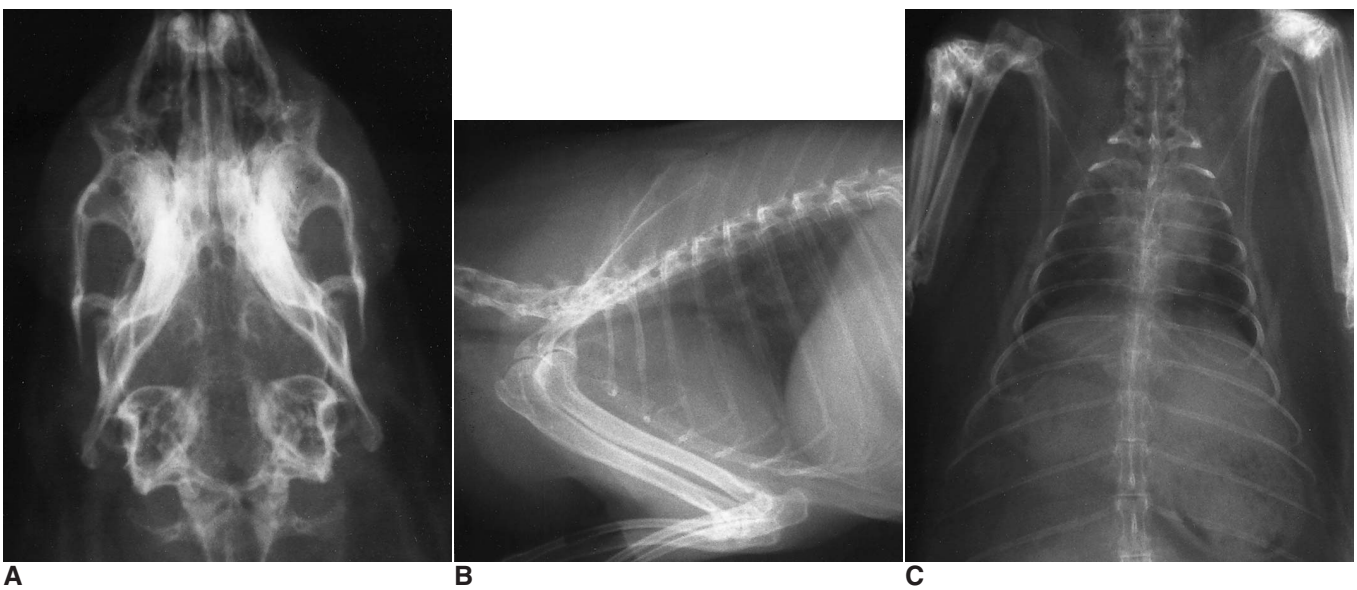


Figure 17-8 Radiographs of a normal 7-year-old rabbit. **A,** Dorsoventral view of the head showing normal turbinates, sinuses, and tympanic bullae. **B,** Lateral view of the thorax showing normal heart and lungs. **C,** Dorsoventral view of the thorax.

eliminated *P. multocida* infection in diseased rabbits.[18] High tissue concentrations of ciprofloxacin were found in kidney, lung, liver, spleen, and muscle. Penicillin (24,000 U/kg) penetrated easily and remained at high levels in the pleural space of rabbits with empyema caused by *P. multocida*.[35] I have had success with some acute pasteurellosis cases and mandibular abscesses using penicillin G benzathine/penicillin G procaine (40,000 IU/kg SC q24h × 2 weeks, then q48h × 2 weeks or longer), and with chronic cases of pasteurellosis using enrofloxacin (5-10 mg/kg PO q12h) or chloramphenicol (50 mg/kg PO q12h) for extended periods (2-3 months). Signs of disease were eliminated and antibody titers diminished. Some owners are willing to use antibiotics in the long term to improve the health and extend the lives of their pets. Adjunct therapy includes instillation of antibiotic drops such as ciprofloxacin ophthalmic drops or gentamicin ophthalmic drops into nares, ear canals, or conjunctival sacs or nebulization with antibiotics. If indicated, lacrimal ducts should be flushed and abscesses surgically removed or lanced and debrided.

Choose an antibiotic based not only on in vitro sensitivity test results but also on the sensitivity of the rabbit's intestinal flora. Enteric dysbiosis can result in fatal enterocolitis or enterotoxemia. Antimicrobial drugs that are less likely to cause this side effect are trimethoprim-sulfa, the fluoroquinolones, chloramphenicol, and tetracyclines. Penicillin given parenterally is less likely to cause dysbiosis than if given orally, and it is the antibiotic of choice for anaerobic infections. The use of any antimicrobial agent in rabbits warrants monitoring. In the event of anorexia, diarrhea, or excretion of abnormal feces, discontinue use of the antibiotic and select a different drug.

CONTROL

Pasteurella-free rabbit colonies were first established by Webster. Webster's methods are still used today and are referred to as "barrier housing."[22] *Pasteurella*-free rabbits are selected by bacteriologic and serologic screening and housed away from

Figure 17-9 This 9-year-old Netherland dwarf lived with chronic but controlled pasteurellosis for years. Its mini-lop companion remained free of pasteurellosis and died when 9 years old from a pulmonary carcinoma.

rabbits of unknown or infected status. Traffic of materials and caretakers from infected to uninfected rabbits is prevented. Cesarean derivation and fostering of kits onto *Pasteurella*-free does is another method of establishing a *Pasteurella*-free colony. Early weaning, with or without the use of antimicrobial drugs for infected does, can yield *Pasteurella*-free weanlings.

Rabbits available at pet stores are not likely to be from *Pasteurella*-free colonies. A rabbit recently acquired from a pet store should be examined, tested for *P. multocida* infection, and, if infected, treated with antibiotics. Elimination of infection may be easier in young rabbits, before disease becomes chronic. If rhinitis is severe and exudate is being expelled by sneezing, isolate the affected animal from other rabbits and ensure that infectious exudate is not spread by fomites. Transmission from rabbits with chronic pasteurellosis is less common than from those acutely affected. Some infected rabbits have lived in relatively close contact with uninfected rabbits and have not transmitted the organism (Fig. 17-9). Germicidal agents that are effective against *P. multocida* include a 10% solution of sodium hypochlorite 5.25%, 1 oz/gal of 2% chlorhexidine diacetate, and 2 mL/gal of 20% benzalkonium chloride; 70% alcohol is not effective. Controlling the spread of infection in the host depends on proper diet, avoidance of stress or changes in ambient temperature, and good husbandry practices, including good ventilation, as well as treatment with antibiotics.

The principles of controlling pasteurellosis also apply to controlling other bacterial infections. In homes where many rabbits reside, new rabbits should be quarantined until their disease status is known. Those with chronic infections can be housed together and cared for after those without disease have received care.

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